Acetals of 1-aryl-2,2-dimethyl-1,3-propanediols synthesis and use as chiral auxiliary

Ebens, Rijko Hendrik Ebe

CHAPTER 6
BROMINATION OF- AND CATALYTIC ADDITIONS TO 2-ALKENYL-4-ARYL-5,5-DIMETHYL-1,3-DIOXANES

6.1 INTRODUCTION

A few remaining subjects will be presented in this last chapter. The following reactions of 2-alkenylacetals **2.19** will be discussed: (1) addition of molecular bromine, (2) osmiuntetroxide catalyzed cis-dihydroxylation, and (3) allylic alkylation catalyzed by Pd(O).

Unpromising results on the first two subjects caused us to decide not to pay more than exploratory attention to these reactions. The allylic alkylation reactions required the synthesis of some α,β-unsaturated-γ-acetoxy aldehydes. Although these syntheses had been described previously, repetition and optimalization led to time consuming problems. The initial results on the allylic alkylation reactions are very promising and further research is necessary to explore the full scope of this approach.

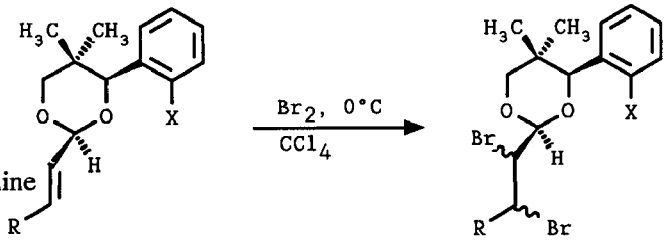
6.2 REACTION OF 2-ALKENYLACETALS 2.19 WITH BROMINE

Addition of molecular bromine to carbon-carbon double bonds proceed through an electrophilic mechanism, provided that no source of radicals is present.[1] The addition takes place in an anti-fashion and is normally stereospecific, especially in solvents of low polarity. The initially formed cyclic bromonium intermediate is attacked from the opposite side of the double bond by a bromide ion. The ionic nature of this bromine addition to alkenes manifests itself in specific cases where rearrangement products and partially acetoxy substitution (in acetic acid as solvent) were found.[1-3] It was also observed that the rate of the addition is susceptible to the electronegativity of the substituents. Steric influences on the addition rate, however, are only small.

The reactions of 2-alkenylacetals **2.19** with bromine were performed to investigate whether stereoselectivity is possible in such an addition process. The general reaction is depicted in Scheme 6.1.

The reactions were run in carbontetrachloride at 0°C. A solution of bromine in carbon tetrachloride was slowly added to the 2-alkenylacetal **2.19** in CCl_4. The reaction vessel was protected from light to prevent the formation of radicals. During the addition of bromine the reaction mixture coloured light yellow. After normal work-up ($NaHSO_3$-solution), the crude reaction product was analyzed by ^{1}H-NMR spectroscopy and thin layer chromatography. These analyses showed that the addition was quantitative. The dibromides **6.1**, however, tend to eliminate hydrobromic acid upon standing.

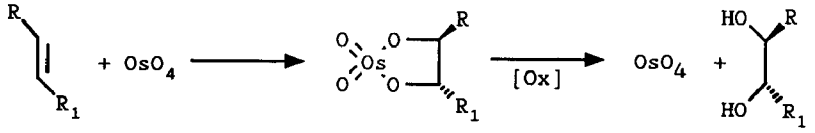
^{1}H-NMR-spectra of the dibromides **6.1** clearly showed that a mixture of diastereomers was formed in a nearly 1:1 ratio. Thin layer chromatography (SiO_2/hexane: ethyl acetate 2:1) of dibromides **6.1** was in agreement with this conclusion. No effect was observed on the diastereomeric ratio when the reaction temperature was lowered (-20°C). No further investigation of the addition of bromine to 2-alkenylacetals **2.19** was performed.



Scheme 6.1 Addition of bromine

6.3 OSMIUM TETRAOXIDE CATALYZED CIS-DIHYDROXYLATION OF 2-ALKENYLACETALS 2.19

The most reliable reagent for the oxidation of alkenes to vicinal cis-diols is beyond doubt osmiumtetroxide.[4] Although originally used in stoichiometric quantities, the high cost and toxicity of this reagent has certainly stimulated the development of several catalytic procedures. In these catalytic alternatives a co-oxidant is used to reoxidize the initially formed osmium (VI) ester to an osmium (VIII) species (Scheme 6.2). The most efficient procedures have been developed by Sharpless et al.[5,6] and Van Rheenan et al.[7] who used t-butyl hydroperoxide and N-methylmorpholine as stoichiometric co-oxidant. Side reactions, that are frequently encountered in other catalytic procedures are (over oxidation and alkene cleavage) are effectively minimized by using the procedures of Sharpless or Van Rheenan.



Scheme 6.2 Cis-dihydroxylation of alkenes by OsO_4

Osmium (VI) esters **6.2** (Scheme 6.2) are intermediates in the cis-hydroxylation reaction. After reoxidation to osmium (VIII) species, hydrolysis takes place in the rate determining step of the process which is defined as "oxidative hydrolysis". The hydrolysis, however, can be accelerated by using slightly basic reaction conditions.[5,6] Sharpless proposed an initial attack of an olefinic carbon on the electropositive osmium center to give the intermediate depicted in Fig. 6.1, which would then rearrange to the osmate ester **6.2**.[8] The existence of such an intermediate has not been confirmed by experimental facts.

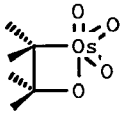
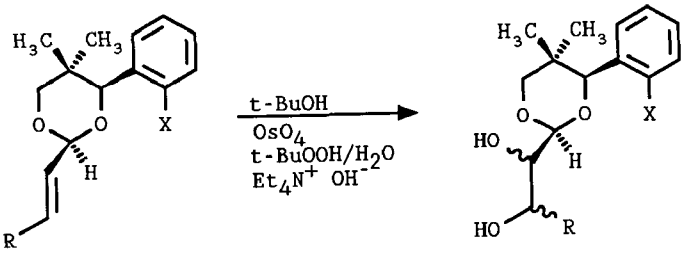


Fig. 6.1

A few studies on asymmetric OsO_4-catalyzed dihydroxylations have been published. Sharpless and coworkers have examined the reaction of alkenes and catalytic quantities of OsO_4 in the presence of chiral amine ligands, in particular cinchona alkaloid derivatives.[9,10] He postulated the existence of a second catalytic cycle, in which the initially formed osmate ester itself acts as a catalyst to provide diols in a low enantiomeric excess.[9] This second cycle could be bypassed by slow addition of the substrate alkene to the other reactants, or by using stoichiometric quantities of osmium tetroxide. The enantiomeric excesses with the optimized procedures varied between 60% to 90%.

The results of Scolastico and Mash are of particular interest, since they used diastereomerically pure cyclic acetals of α,ß-unsaturated carbonyl compounds in the catalytic osmium tetroxide hydroxylation reactions. Scolastico used L-N-benzyloxycarbonylnorephedrine as chiral derivatising agent for α,ß-unsaturated aldehydes, to yield five membered cyclic N,O-acetals.[11] Protected α,ß-diol aldehydes were obtained in diastereomeric excesses of approximately 50%. Mash used the L-(+)-tartaric acid

derived 1,4-di-O-benzyl-L-threitol as chiral auxiliary in the cis-dihydroxylation of 2-cyclopentenone and 2-cyclohexenone.[12] The diastereoselectivities, however, were only moderate (a ratio of approximately 60:40 was obtained). The examples demonstrate the possibilities to cis-hydroxylate diastereoselectively optically pure acetals of α,β-unsaturated aldehydes and ketones.



2.19 a X = H R = C_6H_5

b X = Cl R = CH_3

6.3

Scheme 6.3 OsO_4 catalyzed oxidation of acetals **2.19**

In Scheme 6.3 the osmiumtetroxide cis-dihydroxylation of 2-alkenylacetals **2.19** by the Sharpless procedure[9,10] is illustrated. In the Sharpless procedure 1-5 mole % osmium tetroxide is used as catalyst, together with 1.5 equivalent of t-butylhydroperoxide as co-oxidant. Both commercially available grades of t-butylhydroperoxide (70% or 90%) solutions in water) can be used as such. A water soluble organic base, Et_4NOH or Triton B, was added to facilitate the oxidative hydrolysis of the intermediate osmate esters.

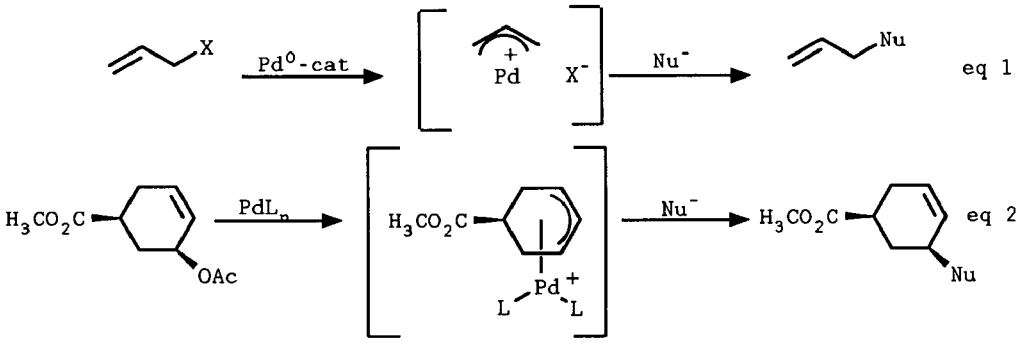
The reactions of 2-alkenylacetals **2.19** with OsO_4, however, were slow at 0°C. Starting material and product were the only observed compounds. No alkene cleavage products were isolated. Entry a (Scheme 6.3, X = H; R = C_6H_5) was the slowest reaction. After 1½ day some starting material was still present. The reaction of entry b (X = Cl; R = CH_3) went to completion in this time. After 2 days of stirring the reaction of entry a was also complete. Starting material was neither observed in the ^{1}H-NMR nor in thin layer chromatography analysis of the crude reaction mixtures. Isolated yields of diols **6.3** are in the range of 70%. ^{1}H-NMR spectra of the isolated diols **6.3**, however, revealed no significant diastereoselectivity. Further research is necessary to determine if this lack of diastereoselectivity in the osmium catalyzed cis-dihydroxylation of 2-

alkenylacetals **2.19**, is inherent for these type of acetals, or if it can be attributed to the action of a second catalytic cycle, as proposed by Sharpless et al.[9].

6.4 PD-CATALYZED ALLYLIC ALKYLATION OF 2-ALKENYLACETALS 2.19

6.4.1 Introduction

The use of transition metal complexes in organic synthesis has provided new possibilities for chemists to accomplish difficult organic transformations and to build multi-functionalized complex molecules.[13] Several catalytic applications have been developed, of which the use of Pd°-complexes in the allylic activation for nucleophilic substitution is a prominent example. The catalytic procedure has been developed by Trost et al. and the basic scheme is shown below (Scheme 6.4, eq. 1).[14]



Scheme 6.4 Pd° catalyzed allylic substitution

Without any intention to give all the details, we will present the most important features of this catalytic transformation. Extensive reviews have been written on this subject.[13,14]

Alkenes that possess a leaving group in an allylic position can be activated by certain Pd°-complexes. Typical leaving groups that are used in this activation of allylic systems are: OAc, halogens, OR, OAr, OC(O)OR, NR_2, SO_2R. Allylic acetates, however, have gained most of the attention.

Soft nucleophiles give the best results. Sulphur and nitrogen nucleophiles can be

used as well as soft carbon nucleophiles like: malonate anion and α-nitro anions. Hard, more basic, carbon nucleophiles can be used (e.g. Grignard reagent) but elimination to form a diene takes place if possible; this means that the allyl-Pd-complex can not have an adjacent hydrogen.

The mechanism has been established fairly well. The allyl Pd-complex is formed by an oxidative addition of the allylic compound to the Pd° catalyst, in which process the leaving group is removed by a S_N2 pathway.[13,15]. Next, the attack on the Pd-allyl complex by the nucleophile regenerates the Pd° catalyst. This reductive elimination is also a S_N2 process, which means that overall the Pd° catalyzed nucleophilic substitution at allylic compounds takes place with retention of configuration, as is shown in Scheme 6.4 (eq. 2).

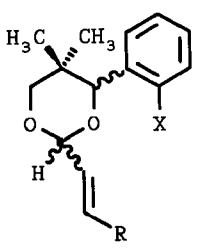
The regioselectivity of the allylic alkylation is often quite predictable. Normally, the nucleophilic attack takes place at the less substituted end of the π-allyl Pd complex.[14c] However, the nature of the nucleophile and the activating ligands play an important role. Important are also electronic effects of the allyl substituents and conformational rigidiy, especially with intramolecular allylic alkylation. Since the nucleophilic subsitution is irreversible with soft carbon nucleophiles the product ratios do reflect the relative rate of their formation.

Enantioselectivity in allylic alkylation reactions can be obtained in principle if a chiral ligand is added to the reaction mixture.[16-18] The ligands used are all bidentate chiral phosphorous compounds. The enantiomeric excesses were not high and varied between 12% and 70%.

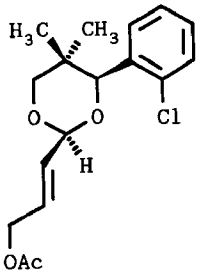
6.4.2 Unsaturated Acetals Used in Pd°-Catalyzed Allylic Alkylation Reactions

We used several diastereomerically pure unsaturated acetals of 1-aryl-2,2-dimethyl-1,3-propanediols **2.19** in allylic alkylation procedures with soft carbon nucleophiles and with tetrakis(triphenylphosphine) Pd°[19] as a catalyst. These acetals are shown in Fig. 6.2. The idea was that in acetals **2.19** one of the ethereal oxygens could serve as a leaving group. However, no literature precedent exists in which an acetal oxygen-carbon bond is cleaved in such a catalytic process. We could not a priori foretell whether a second oxygen atom at the allylic carbon bearing a leaving group would activate or deactivate

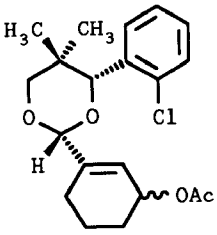
the system. We did anticipate an enhanced stability for the Pd-allyl complex as a result of the electron-donating ability of the oxygen substituent.



2.19



6.4

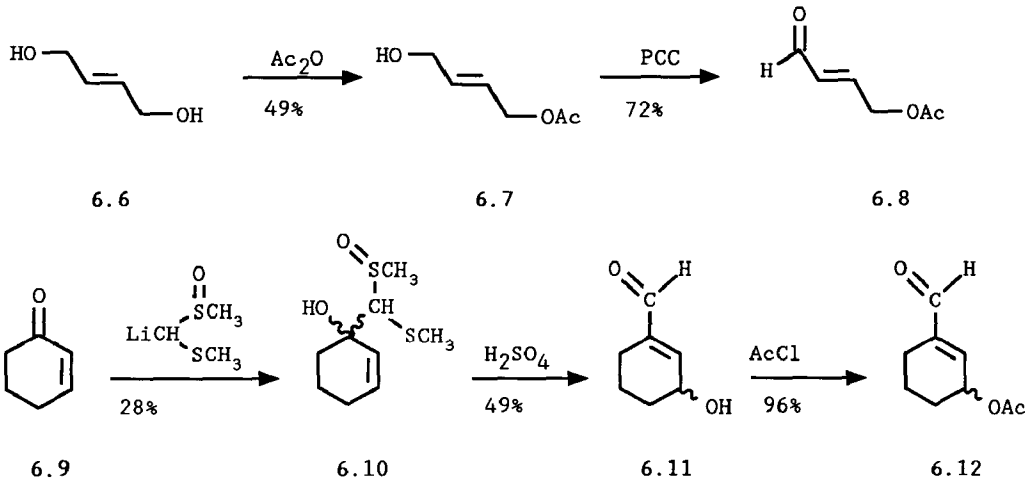


6.5

Fig. 6.2 Acetals used in Pd° catalyzed nucleophilic substitution reactions

Acetals **6.4** and **6.5** possess an allylic acetate as potential leaving group. Several extra problems arose with the design of these systems. In the first place, we needed a synthetic method for γ-acetoxy-α,ß-unsaturated aldehydes. However, no generally applicable route to these compounds exists, and each derivative must be synthesized from a suitable and available precursor. A second question concerns the regioselectivity of the Pd°-catalyzed reaction. In acetal **6.4**, alkylation at the terminus of the allyl system does not result in the formation of a new chiral center; so this system must be alkylated at the carbon adjacent to the acetal carbon in order to be effective. On the basis of steric considerations we had our doubts if this would indeed take place. Acetal **6.5** is more suitable with respect to the regioselectivity, since alkylation at either end of the allylic system creates a new chiral center. The syntheses of both γ-acetoxy-α,ß-unsaturated aldehydes **6.8** and **6.12** is outlined in Scheme 6.5. The syntheses were carried out by Mr. R. Sjouken according to literature procedures.[20]

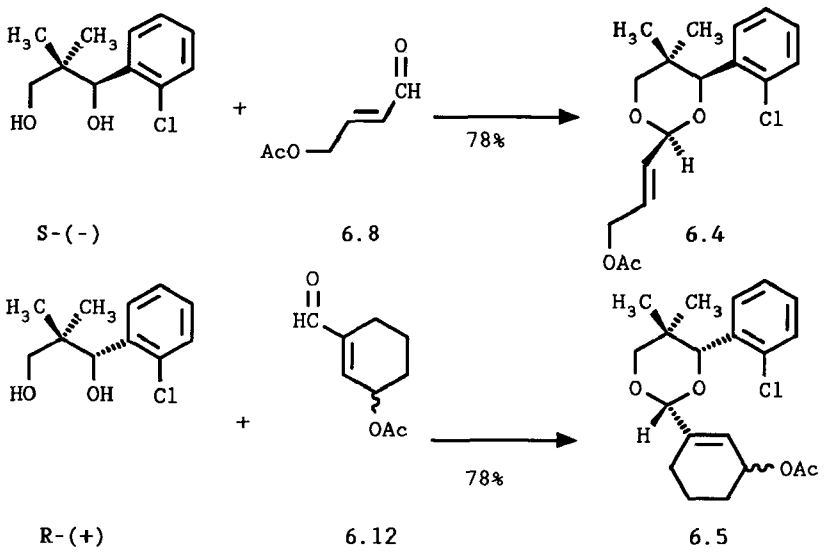
4-Acetoxy-2-butenal **6.8** was prepared in two steps from 1,4-dihydroxy-2-butene. Reaction with 1 equivalent acetic anhydride afforded mono-acetoxy **6.7**, which gave the target molecule **6.8** upon reaction with PCC.[21] Although the product contained some cis aldehyde it was not further purified, since both the cis and trans isomer will result in the formation of the same Pd-allyl complex.[13,14]



Scheme 6.5 Synthesis of γ-acetoxy-α,β-unsaturated aldehydes

The synthesis of 1-formyl-3-acetoxycyclohexene **6.12** was described by Ogura,[22] and started from 2-cyclohexenone **6.9**. The key step is the 1,2-addition of the anion of methyl methylsulfinyl methylsulfide. The ratio of 1,2 versus 1,4 adduct was 91:9 when the reaction was performed in THF at -78°C. The 1,2-adduct could be obtained chemically pure by crystallization. However, we have no idea if and how this crystallization affected the ratio of the two diastereomeric pairs of enantiomers. Treatment of **6.10** with excess of sulfuric acid in diethylether resulted in deprotection of the S,S-acetal moiety and simultaneous a rearrangement to 1-formyl-3-hydroxycyclohexene **6.11** took place. Acylation of the 3-hydroxyl substituent in **6.11** gave the target molecule 1-formyl-3-acetoxy cyclohexene **6.12** as racemic mixture.

Both aldehydes **6.8** and **6.12** were acetalized by reaction with S-(-)- or R-(+)-(o-chlorophenyl)-2,2-dimethyl-1,3-propanediol according to the standard procedure used in Chapter 2 (Scheme 6.6). The chemical yields of these reactions are in the same range as formed for other aldehydes (see Chapter 2). ^{1}H-NMR and ^{13}C-NMR spectra of **6.4** and **6.5** showed that in both compounds the 1,3-dioxane ring occurred in one conformation. NOESY-spectra revealed that in both compounds the 2-alkenyl- and the 4-(o-chlorophenyl)-substituent had assumed an equatorial position. This result is in agreement with our conclusion in Chapter 2 about the conformations of acetals **2.19**, which were derived from 1-aryl-2,2-dimethyl-1,3-propanediols.



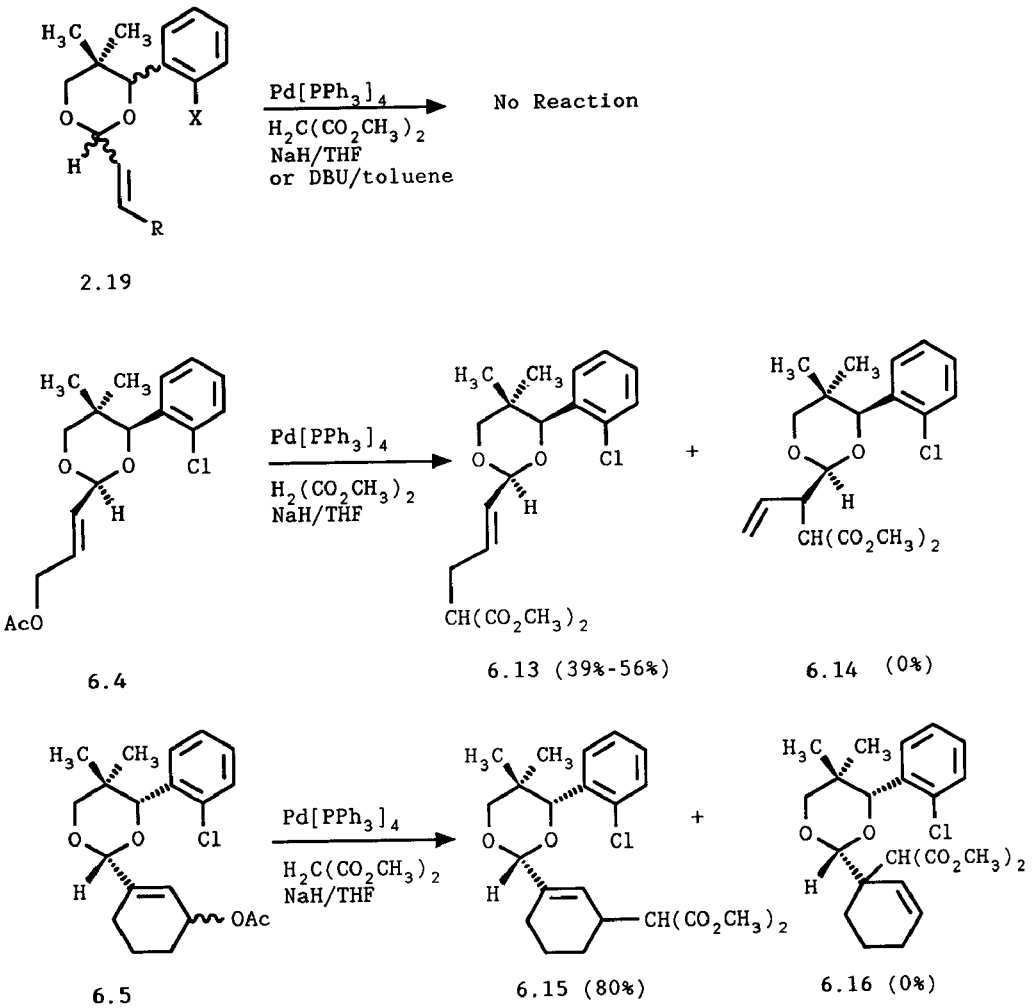
Scheme 6.6 Synthesis of acetals **6.4** and **6.5**

6.4.3 Pd°-Catalyzed Allylic Alkylation of 2-Alkenyl Acetals

2-Alkenyl acetals **2.19**, **6.13** and **6.14** were subjected to allylic alkylation reactions (Scheme 6.7). Palladium tetrakistriphenyl phosphine was used as catalyst and the dimethyl malonate anion served as nucleophile in all the reactions. Procedures developed by the Trost group were used for the alkylation reactions.[23,24] One procedure used the malonate anion that was previously generated in THF with sodium hydride and added all at once to a solution of the acetal, the catalyst and extra triphenylphosphine, also in THF. In the second procedure all reactants are dissolved in toluene, and DBU, a bicyclic strong nucleophilic amine is used as base. Reaction temperatures are 60-65°C (THF was refluxed; toluene was stirred in a thermostated oil bath).

Acetals **2.19** appeared to be inert towards the above mentioned reaction conditions. Unchanged starting material was recovered almost quantitatively. No traces of substitution products or any other acetal cleavage products were found. The γ-acetoxy acetals **6.4** and **6.5** reacted cleanly with the sodium malonate, in the presence of 5 mole % $Pd(PPh_3)_4$. The regioselectivity was entirely on the side of the allyl system opposite to the 1,3-dioxane chiral auxiliary; since only **6.13** and **6.15** were isolated and no traces of the regioisomers **6.14** and **6.16** were observed. The chemical yields of **6.13** varied between

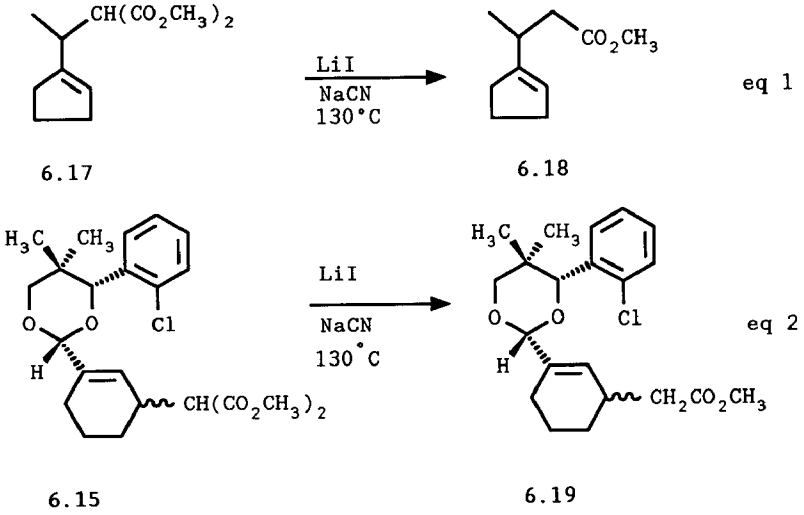
39-56%. These low yields, however, are due to isolation problems, since almost no starting material was present in the crude reaction product. Acetal **6.5** reacted more slowly under the same conditions as acetal **6.4** did. Therefore, the reaction of acetal **6.5** was performed in 1,4-dioxane as solvent at reflux temperature (bp. 101°C, 20 h reflux and chemical yield 80%).



Scheme 6.7 Allylic alkylation of acetals **2.19**, **6.4** and **6.5**

In the formation of **6.13** no new chiral center is created and therefore the reaction of γ-acetoxy acetal **6.4** has no significance for our goals, other than establishing the regioselectivity of this reaction. In acetal **6.5** the leaving group is attached to a chiral carbon center, but both configurations are present. The ^{1}H- and ^{13}C-NMR spectra of the substitution product **6.15** showed that **6.15** was formed in diastereomeric excess of 95%.

Trost has established the enantiomeric excess of **6.17**, which compound is also a Pd-catalyzed allylic substitution product, by decarboxylation to the monoester **6.18**.[16] ^{1}H-NMR of **6.18** in the presence of the chiral shift reagent $Eu(hfc)_3$ gave the ee. of **6.18** from the integration of carbomethoxy doublet (eq. 1, Scheme 6.8).

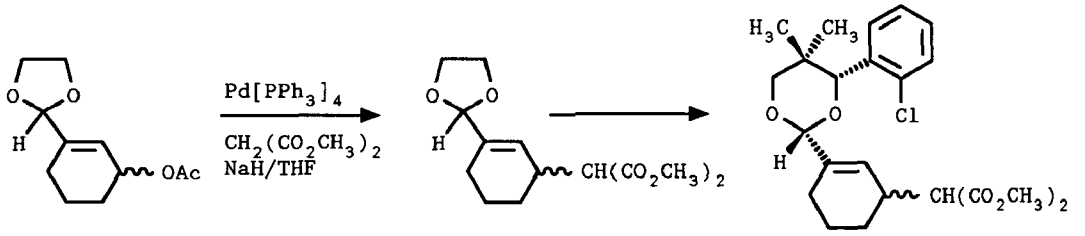


Scheme 6.8 Decarboxymethylation of malonic diester derivatives

The acetal **6.15** was decarboxymethylated by LiI/NaCN in 67% yield by the procedure of Trost[16] (eq. 2, Scheme 6.8). The ^{1}H-NMR of **6.19** recorded in the presence of $Eu(hfc)_3$, showed one peak for the carbomethoxy group, indicating a d.e. ≥ 95%.

For further confirmation we performed the next control experiment (Scheme 6.9). 1-Formyl-3-acetoxy cyclohexene **6.12** was acetalized with ethylene glycol to yield acetal **6.22.** This γ-acetoxy acetal **6.19** was used in a Pd-catalyzed allylic alkylation with the soldium malonate to give the substituted compound **6.20.** Trans-acetalization with R-(+)-(o-chlorophenyl)-2,2-dimethyl-1,3-propanediol yielded acetal **6.15**, in which the new chiral

carbon is now present with both possible absolute configurations. The ^{1}H- and ^{13}C-NMR spectra of this compound clearly differ from the previously recorded spectra of the assumed diastereomeric pure acetal **6.15** (Scheme 6.7). This means that our conclusion about the diastereomeric excess of **6.15**, which was based on these NMR-spectra, is correct.



6.22 6.23 6.15

Scheme 6.9

6.4.4 Rationalization of the Diastereoselectivity in the Pd-Catalyzed Allylic Substitution of γ-Acetoxy-α,β-Unsaturated Acetal 6.5

Rationalization of the stereochemical result of the reaction of γ-acetoxy-α,β-unsaturated acetal **6.5** with the sodium malonate under Pd°-catalysis is rather speculative, since the absolute configuration of the newly created chiral center is not known. Nevertheless, any reasonable explanation for the high diastereomeric excess must be built on the assumption that only one Pd-allyl complex exists. We tried to visualize which Pd-allyl complex would be most stable by looking at CPK models. We believe that Fig. 6.3 gives a plausible picture of this complex.

The π-allyl system of the complex is arranged perpendicular to the acetal carbon-hydrogen bond.* This creates a pocket on the si-face of the allyl system. The nucleophile

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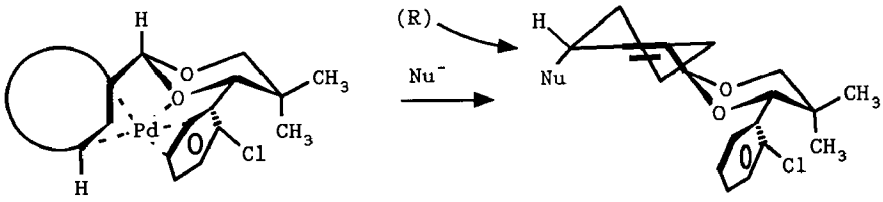
* Hehre calculated minimum energy conformations of 1-butene-2-ol and 3-methoxy-1-butene and found that there exists a favoured conformation in which the double bond is eclipsed with the allylic hydrogen.[25] Without suggesting a fully analogy, we feel that the conformation of the 2-alkenyl side chain π-

attacks from the re-face of the π-allyl system, and ends up in a pseudo-equatorial position (Fig. 6.3). This means that the absolute configuration would be (**R**). The existence of the above mentioned Pd π-allyl complex would fully explain the observed diastereoselectivity in the Pd° catalyzed allylic nucleophilic substitution γ-acetoxy-α,β-unsaturated acetal **6.5**.



6.20 Nu = $^{-}CH(CO_2CH_3)_2$ 6.15

Fig. 6.3 Pd°-allyl complex in the alkylation of **6.5**

To further substantiate this theory it would be necessary to establish the absolute configuration of the new chiral center. Deprotection of the acetal **6.15** and transformation of the substituted 1-formylcyclohexene moiety to a compound of which the absolute configuration and optical purity are known is the principal method to attain this goal. However, this work had not yet been undertaken.

6.5 CONCLUDING REMARKS

Three types of reactions of 2-alkenyl acetals **2.19** were described in this chapter: the addition of molecular bromine, the osmium tetroxide catalyzed cis-dihydroxylation, and the allylic alkylation which is catalyzed by palladium(o) complexes.

The addition of molecular bromine proceeded without any diastereoselectivity. Moreover, the addition products **6.1** all showed a tendency to eliminate hydrobromic acid. We spent no more time on this reaction.

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system prior to the oxidative addition of Pd(O) is perpendicularly arranged to the acetal carbon-hydrogen bond.

The osmium tetroxide catalyzed cis-dihydroxylation of 2-alkenyl acetals **2.19** was slow, but the diols **6.3** were obtained in moderate yields and in a low (5-10%) diastereomeric excess. Nevertheless, we believe that this reaction possesses some potential to increase the de.'s Variation in the organic base that is used can possibly improve the rate of the oxidative hydrolysis of the intermediate osium(VI) ester. A faster hydrolysis of the osmium (VI) ester can perhaps suppress possible catalytic activity of this intermediate.[10] A slow addition of the 2-alkenylacetal **2.19** to the other reactants in solution may also help us to solve the question whether a second catalytic cycle exists.

Simple 2-alkenyl acetals **2.19** are not suited for allylic alkylation under Pd° catalysis. The presence of a second alkoxy group on the same allylic carbon apparently diminishes the leaving group ability of the first alkoxy group. Introduction of a γ-acetoxy substituent, as in **6.4** and **6.5** (Fig. 6.1) gave systems that are reactive under the conditions that are normally used in these type of reactions. However, complete regioselectivity at the allylic carbon away from the chiral auxiliary was observed. In **6.4** this regioselectivity resulted in the substitution at a non-chiral carbon atom. A structure for a palladium allyl complex derived from **6.5** was proposed and in this complex the terminal allylic carbon is prochiral. NMR analysis of the product showed us that the substitution had proceeded with a near absolute diastereoselectivity. The absolute configuration at the new chiral center needs to be established.

6.6 EXPERIMENTAL PART

For general remarks, see the Experimental Parts of the preceeding chapters.

4-Acetoxy-2-butenal (**6.8**) was prepared from 1,4-dihydroxy-2-butene in two steps by standard literature procedures.[26,27] 1-Formyl-3-acetoxy cyclohexene (**6.12**) was synthesized according to a procedure described by Oguna.[22] $Pd[PPh_3]_4$[19] was synthesized analogous to a literature procedure.

(2S,4S)-(+)-2-(3'-Acetoxy-1-transpropenyl)-4-(o-chlorophenyl)-5,5-dimethyl-1,3-dioxane (6.4): was synthesized from S-(-)-1-(o-chlorophenyl)-2,2-dimethyl-1,3-propanediol and 4-acetoxy-2-butenal **6.8** by the standard procedure described in Chapter 2.

c.y. 78%

b.p. 215°C (0.5-0.6 mmHg bulb-to-bulb).

^{1}H-NMR ($CDCl_3$/TMS): δ 0.76 (s, 3H); 1.03 (s, 3H); 2.04 (s, 3H); 3.72 (s, 2H); 4.59 (d, 2H); 5.09 (s, 1H); 5.18 (d, 1H); 5.88 (dvd, 1H); 6.05 (dvt, 1H); 7.2-7.6 (m, 4H);

^{13}C-NMR ($CDCl_3$): δ 19.1 (q); 20.7 (q); 21.7 (q); 35.2 (s); 63.4 (t); 78.5 (t); 81.8 (d); 100.4 (d); 126.1 (d); 128.4 (d); 128.6 (d); 128.9 (d); 129.4 (d); 130.2 (d); 132.7 (s); 135.5 (s);

170.3 (d).

(2R,4R)-(-)-2-(3'-Acetoxy-1'-cyclohexene)-4-(o-chlorophenyl)-5,5-dimethyl-1,3-dioxane (6.5) was synthesized from R-(+)-1-(o-chlorophenyl)-2,2-dimethyl-1,3-propanediol and 1-formyl-3-acetoxy-cyclohexene **6.12** according to the standard procedure described in Chapter 2.
c.y. 78% $[\alpha] = {}^{20}_{578}$ -5.6 (c 0.50 $CHCl_3$).
^{1}H-NMR ($CDCl_3$/TMS): δ 0.74 (s, 3H); 1.00 (s, 3H); 1.6-1.8 (m, 4H); 1.97 and 1.98 (2xs, 3H); 2.2-2.4 (m, 2H); 3.70 (s, 2H); 5.00 and 5.01 (2xs, 1H); 5.05 and 5.10 (2xs, 1H); 5.26 (br s, 1H); 5.90 (br s, 1H); 7.2-7.5 (m, 4H);
^{13}C-NMR ($CDCl_3$): δ 18.5 (t); 19.2 (q); 21.2 (q); 21.7 (q); 22.9 (t); 28.1 (t); 35.3 (s); 67.7 (d); 67.8 (d); 78.5 (t); 81.7 (d); 103.5 (d); 124.1 (d); 126.2 (d); 128.6 (d); 129.0 (d); 130.2 (d); 132.7 (s); 140.7 (s); 170.5 (s).

General Procedure for Pd Catalyzed Allylic Alkylation with Sodium malonate.

All reactions were carried out under dry nitrogen and in solvents that were dried prior to use by standard procedures.

A sodium hydride dispersion was washed in pentane and then submerged in THF. One equivalent of dimethylmalonate THF was added dropwise and the resulting mixture was stirred magnetically for 5 min. 1.1 Equivalent of this solution was added all at one to a THF solution containing: 1.0 equivalent of allylic acetate; 1.0 equivalent triphenylphosphine; and 5 mole% tetrakistriphenylphosphine palladium(o). After stirring for 15-20 min. the solution was refluxed for 20 h. To the cooled reaction mixture was added n-hexane to precipitate the triphenylphosphine and the palladium remainders, these solids were removed by filtration. An alternative to remove the palladium complex and the phosphines is to filtrate the reaction mixture over a short silica column. The resulting solution was evaporated in vacuo, in order to remove the excess dimethyl malonate. The crude product can be purified by column chromatography or by bulb-to-bulb distillation.

(2S,4S)-2-(2'-Propenyldimethylmalonate)-4-(o-chlorophenyl)-2,2-dimethyl-1,3-dioxane (6.13) was synthesized by the procedure described above.
b.p. 195°C (0.04 mmHg) bulb-to-bulb
c.y.: 39-56%.
^{1}H-NMR ($CDCl_3$/TMS): δ 0.68 (s, 3H); 0.94 (s, 3H); 2.59 (dvd; 2H); 3.39 (t, 1H); 3.64 (s, 2H); 3.66 (s, 6H); 4.99 (s, 1H); 5.02 (d, 1H); 5.6-5.9 (m, 2H); 7.1-7.4 (m, 4H);
^{13}C-NMR ($CDCl_3$): δ 19.2 (q); 21.7 (q); 31.2 (t); 35.2 (s); 51.0 (d); 52.4 (2xq); 78.5 (t); 81.8 (t); 101.0 (d); 126.1 (d); 128.6 (d); 129.0 (d); 129.7 (d); 130.2 (d); 130.4 (d); 132.7 (s); 135.6 (s); 168.9 (s).

(2R,4R)-2-(i-cyclohexene-3'-dimethylmalonate-4-(o-chlorophenyl)-5,5-dimethyl-1,3-dioxane (6.15) was synthesized by the general procedure. However, 1,4-dioxane was used as solvent and 3 equivalents of dimethylmalonate were used. The product was purified by column chromatography.
c.y. 80%.
$[\alpha]^{20}_{578}$ = 28.9° (c 0.48, $CHCl_3$).
^{1}H-NMR ($CDCl_3$/TMS): δ 0.70 (s, 3H); 0.95 (s, 3H); 1.2-1.3 (m, 1H); 1.5-1.6 (m, 1H);

1.7-1.8 (m, 2H); 4.99 (s, 1H); 5.69 (br s, 1H); 7.1-7.4 (m, 4H);
^{13}C-NMR ($CDCl_3$): δ 19.1 (q); 20.6 (t); 21.6 (q); 22.5 (t); 26.4 (t); 35.0 (d); 35.1 (s); 51.2 (q); 56.4 (d); 78.3 (t); 81.4 (d); 104.2 (d); 126.0 (d); 126.5 (d); 128.5 (d); 128.9 (d); 130.1 (d); 132.6 (s); 135.8 (s); 137.9 (s); 168.3 (s); 168.5 (s).

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